§112

Claims 1 and 2 stand rejected under §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the invention. The Examiner took the position that the term "desired target solubility" cannot be determined from the claim.

The Examiner is earnestly requested to reconsider and withdraw the rejection. The claim language is "equal to or greater than a desired target solubility". The phrase "desired target solubility" is abundantly explained starting at page 4, line 25, as being a minimum (i.e., a thresshold level) of solubility required for a therapeutic need. A hypothetical example is given to illustrate that which is intended by Applicant for the phrase (page 4, lines 27-32). It is explained starting at the top of page 5 that a target solubility need not be the maximum solubility determined, but may simply be an intermediate value above the target solubility but below the maximum equilibrium solubility determined for the series. It is well accepted that claims are interpreted in light of the specification. It is Applicant's position that the term "desired target solubility" was completely clear and distinct without the abundant explanation given in Applicant's specification, but that, especially in light of the explanation (and exemplification) of "desired solubility" supplied by Applicant in the specification, one skilled (as §112 requires) in the art, would surely find the claims to be clear and distinct, and have no difficulty understanding the metes and bounds of the subject matter claimed.

§103(a)

Again, it is emphasized that the invention is based, *inter alia*, on the recognition by Applicant that different salts of a given compound can have different solubilities in the same cyclodextrin. Without the recognition that such solubilities can differ, a method for determining a solubility in excess of a desired target solubility cannot be obvious. Neither Szejtli nor Bryant contain any such recognition.

Szejtli doesn't deal with salts at all. Szejtli discloses inclusion complexes of a single compound, indomethacin. In this regard, the following is stated at column 2, lines 26-33, in referring to an article from the prior art (Takeo and Kuge, Agric. Biol. Chem., 34, 1787, 1970)):

> [c]onsequently it was not the preparation of an Indomethacin-cyclodextrin complex that was disclosed in the above-mentioned article, but rather a physical mixture of the ammonium salt of Indomethacin and cyclodextrin as the product. According to our observations salts of

> Indomethacin cannot be incorporated in a cyclodextrin inclusion complex, the salts prove to be too ionic, i.e. hydrophilic.

Szejtli further states, at column 2, lines 34-36:

> The above mentioned Japanese authors set as an aim to prepare a 1:1 molar complex, but they did not succeed.

Thus, the only mention in Szejtli of anything having to do with salts/cyclodextrins is in connection with a reference to an apparently failed experiment with an indomethacin salt in a prior art journal article. Szejtli himself is not concerned with indomethacin salts (or salts of any other therapeutic compounds), however, and discloses nothing relating to salts that has anything to do with Applicant's invention. Szejtli himself appears interested only in cyclodextrin complexes of the non-salt (free) form of indomethacin. He does not disclose a series of salts nor any method for determining solubilities in cyclodextrin as between different salts. Accordingly, Szejtli discloses nothing relating to a salt located by Applicant's method, or anybody else's method for that matter. It is simply not possible that Szejtli could render Applicant's invention obvious.

It is noted that the Examiner commented, on page 3 of the Office Action, that:

> "Screening a variety of drug salts for solubility is routine and would have been obvious to the person of ordinary skill in the art wanting to optimize the water solubility of a drug."

Again, Applicant notes that the invention doesn't merely relate to the "water solubility of a drug", but relies on the recognition that different salts of a compound can have different solubilities in the same cyclodextrin. Attention is directed to the discussion at page 2, lines 14-27, from page 5, line 31 to page 7, line 10 in this regard. Szejtli contains no disclosure relating to the solubilities of different salts in a given cyclodextrin, nor does Szejtli contain even the remotest indication or suggestion that such differences in solubility would exist.

It is accordingly respectfully requested that the rejection under §103(a) over Szejtli be withdrawn.

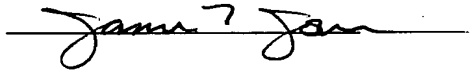
Bryant discloses a series of benzothiophenes or a salt thereof which have low water solubilities. Bryant further discloses a list of acid salt counterions starting at column 3, line 14. Specific salts are not disclosed in this section. The claims and disclosure feature an aqueous inclusion complex containing the benzothiophene *per se* or a salt thereof. Bryant thus appears to be neutral as to whether his inclusion complexes are made with his compound of formula (I) or with a salt thereof, and therefore contains no particular teaching that a salt should be used as opposed to the impliedly neutral compound. **Importantly with respect to the present application,**

there is no disclosure or teaching in Bryant that any salt of a given compound would be any more or less soluble in a given cyclodextrin than any other salt in the same cyclodextrin. Thus there is no recognition in Bryant that different salts of the same compound can have different solubilities in a given cyclodextrin, i.e., of the finding that underlies Applicant's invention. Indeed, the only specific salt Bryant actually discloses is the hydrochloride salt of a particular benzothiophene known as raloxifene (column 3, lines 58-62; Example 1; the claims). Thus, Bryant (1) never suggests that any particular salt of a compound of formula (I) is any more soluble in a given cyclodextrin than any other salt made with any other counterion also disclosed therein, (2) never touches on how such a salt would be located, and (3) never even remotely suggests the possibility or feasibility of doing so. Bryant neither discloses, suggests, nor motivates anything relating to Applicant's method, and could not without a recognition of the finding mentioned above. Without such suggestion or motivation it is simply not possible for Bryant to render Applicant's method obvious. Accordingly, it is respectfully requested that the rejection of claims 1-3 be withdrawn.

In view of the foregoing comments and amendments it is believed this application is in condition for allowance. A Notice of Allowance is accordingly courteously solicited.

Respectfully submitted,

Date: November 17, 1999



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